

In re Application of: Michal DANIELY et al
Serial No.: 10/771,440
Filed: February 5, 2004
Office Action Mailing Date: April 29, 2010

Examiner: DUFFY Bradley
Group Art Unit: 1643
Attorney Docket: 26003
Confirmation No.: 3178

92. (Cancelled)

93. (New) The method of claim 72, wherein said nucleated cells of the voided urine sample are cyto-centrifuged at a cell density of 300-500 cells per mm² prior to step (a).

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REMARKS

Reconsideration of the above-identified Application in view of the amendments above and the remarks following is respectfully requested.

Claims 72, 73 and 82-92 are pending in this Application. Claims 72, 73, 82, 83, 85 and 87-92 have been rejected under 35 U.S.C. §102(b). Claims 72, 73, 84, 86-92 have been rejected under 35 U.S.C. §103(a). Claims 72, 73 and 87 have been amended herewith. Claims 83, 85, 86, 88, 90 and 92 have been cancelled herewith. New claim 93 has been added herewith.

35 U.S.C. §102 Rejections

The Examiner has maintained the rejection of claims 72, 73, 82, 83, 85 and 87-92 under 35 U.S.C. §102(b) as being anticipated by Inoue et al. (Urol. Res. 28: 57-61, 2000). Specifically, the Examiner states that while Inoue et al., performed cytology on voided urine, the teachings of Inoue et al., establish that the same single cells obtained from exfoliated urine samples obtained by catheterization comprise both single cells having a morphological abnormality of a transitional cell carcinoma cell stained by Giemsa, and the same single cells having a chromosomal abnormality of a transitional cell carcinoma stained by FISH. The Examiner states that as set forth in Figures 2a and 2b, Giemsa stained single cells obtained via exfoliated urine samples are identified as having morphological abnormalities such as a considerable dark appearance of a cell or an irregular nuclear border as compared to transitional epithelial cells with a normal morphology, and those same single cells are identified as having chromosomal abnormalities, i.e., loss of chromosome 9; in this case the description of Figure 2b explicitly states that the same nuclei in the same cells are stained for FISH as those stained by Giemsa; and that a similar situation is in Figures 3a and 3b; accordingly, the methods of Inoue et al., which stain and identify the same single cells as having both morphological abnormalities as stained by Giemsa and chromosomal abnormalities as stained by FISH are materially and manipulatively indistinguishable from the claimed process. Examiner's rejection is respectfully

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traversed. Claims 72, 73 and 87 have been amended herewith. Claims 83, 85, 88, 90 and 92 have been cancelled herewith, thereby rendering moot Examiner's rejections with respect to these claims.

Applicants point that Inoue et al., do not teach or suggest identifying transitional cell carcinoma cells by analyzing a nucleus to cytoplasm ratio of Giemsa-stained transitional epithelial cells and identifying a suspicious transitional carcinoma cell having a high nucleus/cytoplasm ratio as compared to normal transitional epithelial cell, followed by identification of a chromosomal abnormality in the same suspicious cell as in the currently amended claimed invention, since exfoliated urine cells as in Inoue et al., appear in cell clusters (Inoue et al., Page 57, right column, last 3 lines; and images in Figures 1a, 2a and 3a) in which the cell borders are not clear, and thus the nucleus to cytoplasm ratio of a single cell cannot be determined. Thus, analysis of the Giemsa stained exfoliated cells of Inoue et al., cannot result in identification of cells having an abnormal nucleus to cytoplasm ratio since the cell borders in the exfoliated urine sample are not clear. Thus, Inoue et al., classified the urine samples based on cytology analysis performed on the voided urine samples (Inoue et al., Page 58, right column, lines 9-11) and determined the chromosomal abnormalities based on the FISH staining of the exfoliated cells (Inoue et al., Figures 1b, 2b, 3b), i.e., not on the same single cells.

In sharp contrast to Inoue et al., the claimed invention is based on determination of a nucleus to cytoplasm ratio of transitional epithelial cells in a voided urine sample, identification of cells having a suspicious morphology based on a high nucleus to cytoplasm ratio as compared to normal transitional epithelial cells, and determination of FISH abnormalities in suspicious transitional carcinoma cells (based on morphological abnormality), wherein a cell with both abnormal FISH and a high nucleus to cytoplasm ratio is a transitional carcinoma cell. Thus, the method of the claimed invention is novel and non-obvious over the cited art since it teaches, for the first time, identification of transitional carcinoma cells and diagnosis of bladder cancer by analyzing transitional epithelial cells from a voided urine sample at a single cell level, and determining presence or absence of a transitional cell carcinoma based

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on an abnormal high nucleus to cytoplasm ratio and a chromosomal abnormality in the same single cell.

Support for claim amendments:

Claim 72: “voided urine sample” (Page 5, line 23 in the instant application as filed); “analyzing a nucleus to cytoplasm ratio in transitional epithelial cells” (Page 7, lines 28-31 in the instant application as filed); “a morphological abnormality which comprises a high nucleus to cytoplasm (N/C) ratio as compared to a transitional epithelial cell with a normal morphology” (previously filed claims 87-88);

Claim 73: “voided urine sample” (Page 5, line 23 in the instant application as filed);

Claim 92: “cyto-centrifuged at a cell density of 300-500 cells per mm²” (Page 25, lines 14-16 in the instant application as filed);

In view of the above arguments and remarks Applicants believe to have overcome the 35 U.S.C. §102 (b) rejections.

35 U.S.C. §103 Rejections

Inoue in view of U.S. Patent No. 6,418,236

The Examiner has maintained the rejection of claims 72, 73, 84 and 86 under 35 U.S.C. §103(a) as being unpatentable over Inoue et al., in view of U.S. Patent No. 6,418,236 (Ellis et al.). Examiner’s rejection is respectfully traversed.

For clarity, Applicants are describing the teachings of Inoue et al. and U.S. Patent No. 6,418,236 individually but are traversing the rejection with respect to the combination of these references, *infra*. That is, the Applicants are not attacking the references individually, rather addressing the combinations of references as set forth in the instant Office Action.

Applicants arguments with respect to the reference of Inoue et al. are described above.

With respect to U.S. Patent No. 6,418,236, Applicants point that the reference merely discloses a microscope capable of dual imaging.

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Thus, Applicants point that the combined references do not teach or suggest analyzing the nucleus to cytoplasm ratio of a transitional epithelial cell in a voided urine sample, identifying a transitional epithelial cell suspicious as being a transitional carcinoma cell based on a morphological abnormality which comprises a high nucleus to cytoplasm (N/C) ratio as compared to a transitional epithelial cell with a normal morphology, and determining by FISH staining if the morphologically suspicious cell has a chromosomal abnormality, even when using a microscope capable of dual imaging as described in U.S. Patent No. 6,418,236, since based on the teachings of Inoue et al., FISH staining was performed on exfoliated cell clusters which do not enable determination of a nucleus to cytoplasm ratio as in the currently amended claimed invention. Thus, the claimed invention is novel and inventive over the teachings of Inoue et al. and US Patent No. 6,418,236, either alone or in combination.

Inoue in view of Kaplinsky (ASH meeting, 2001)

The Examiner has maintained the rejection of claims 72, 73, 84 and 86 under 35 U.S.C. §103(a) as being unpatentable over Inoue et al., in view of Kaplinsky (ASH meeting, 2001). Examiner's rejection is respectfully traversed.

Applicants arguments with respect to the reference of Inoue et al. are described above.

With respect to Kaplinsky et al., Applicants point that the reference merely discloses a microscope capable of dual imaging.

Thus, Applicants point that the combined references do not teach or suggest analyzing the nucleus to cytoplasm ratio of a transitional epithelial cell in a voided urine sample, identifying a transitional epithelial cell suspicious as being a transitional carcinoma cell based on a morphological abnormality which comprises a high nucleus to cytoplasm (N/C) ratio as compared to a transitional epithelial cell with a normal morphology, and determining by FISH staining if the morphologically suspicious cell has a chromosomal abnormality, even when using a microscope capable of dual imaging as described in Kaplinsky et al, since based on the teachings of Inoue et al., FISH staining was performed on exfoliated cell clusters which do not enable

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determination of a nucleus to cytoplasm ratio as in the currently amended claimed invention.

Inoue et al., in view of Brown et al.

The Examiner has rejected claims 72, 73, 87 and 88 under 35 U.S.C. 103(a) as being unpatentable over Inoue et al., (Urol Res. 28:57-61, 2000), in view of Brown (Urol. Clin. NA., 27:25-37, 2000). Specifically, the Examiner states that while Inoue et al., teach methods of staining, imaging and identifying the same single cells from an exfoliated urine sample obtained via the catheterization as having considerable dark appearance or an irregular border by Giemsa morphological staining as compared to normal transitional cells and staining by FISH to identify chromosomal abnormalities, Inoue does not expressly teach said morphological abnormality being a high nucleus to cytoplasm ratio or an enlarged nucleus. The Examiner further states that Brown et al., teach that other morphological abnormalities that identify transitional cell as suspicious as transitional carcinoma cells include cells with a high nucleus to cytoplasm ratio identified by Papanicolaou stain. The Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to predictably substitute the morphological abnormalities taught by Brown in the methods of Inoue et al., to identify single cells form a urine sample having a high nucleus to cytoplasm ratio or an enlarged nucleus and a chromosomal abnormality to identify the same single cell as transitional cell carcinoma cells in view of these references as a whole. Examiner's rejection is respectfully traversed.

Applicants point that a *prima facie* case of obviousness has not been properly set since the combined references do not teach or suggest the currently amended claimed invention.

Thus, in contrast to Examiner's assertion one of ordinary skills in the art, in view of the teachings of Inoue et al., which teach using exfoliated cells for FISH analysis and voided urine for cytology analysis (i.e., for classification of the voided urine samples), and further in view of Brown et al., who merely describe cytology analysis of voided urine using parameters such as a nucleus to cytoplasm ratio, would

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not have had any motivation to reach to the currently amended claimed invention since the FISH analysis in Inoue et al. was performed on exfoliated cell clusters and not on isolated single cells which are obtained from a voided urine sample as in the claimed invention. Thus, even if desired, the nucleus to cytoplasm ratio as taught in Brown et al., could not be determined in the exfoliated urine cell clusters of Inoue et al., since the cells selected for FISH analysis by Inoue et al., were those present in cell clusters (Inoue et al., Page 57, right column, last 3 lines), and not on single cells from voided urine sample which enable determination of a nucleus to cytoplasm ratio and identification of a morphologically abnormal a high nucleus to cytoplasm ratio as compared to normal transitional epithelial cells as in the currently amended claimed invention.

Inoue et al., in view of Sokolova et al.

The Examiner has rejected claims 72, 73, and 89-92 under 35 U.S.C. 103(a) as being unpatentable over Inoue et al., (Urol Res. 28:57-61, 2000), in view of Sokolova et al., (J. Mol. Diag. 2:116-123, 2000). Specifically, the Examiner states that while Inoue et al., teach methods of staining, imaging and identifying the same single cells from an exfoliated urine sample obtained via catheterization as having a morphological abnormality by Giemsa morphological staining as compared to normal transitional cells and staining by FISH to identify polyploidy of chromosome 7 and loss of chromosome 9 which includes loss of the 9p21, Inoue et al., does not expressly teach FISH stains that identify polyploidy of chromosome 3 and chromosome 17 in transitional carcinoma cells and do not teach a FISH stain that is directed at the 9p21 locus; The Examiner states that the deficiency is made up for the teaching of Sokolova et al which teach other chromosomal abnormalities include polyploidy of chromosome 3, 17 and loss of 9p21. The Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to predictably substitute the chromosomal abnormalities taught by Sokolova et al., in the methods of Inoue et al., to identify single cells from a urine sample having a morphological abnormality and a polyploidy of chromosome 2, 17 or

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loss of 9p21 to identify the same single cells as transitional cell carcinoma cells in view of these references as whole. Examiner's rejection is respectfully traversed.

Applicants point that a *prima facie* case of obviousness has not been properly set since the combined references do not teach or suggest the currently amended claimed invention.

Thus, in contrast to Examiner's assertion one of ordinary skills in the art, in view of the teachings of Inoue et al., which teach using exfoliated cells for FISH analysis and voided urine for cytology analysis (i.e., for classification of the voided urine samples), even in view of the teachings of Sokolova et al., who teach FISH polyploidy of chromosomes 2 and 17 or loss of 9p21, would not have had any motivation to reach to the currently amended claimed invention since the FISH analysis in Inoue et al. was performed on exfoliated cell clusters which do not enable analysis of a nucleus to cytoplasm ratio for identification of transitional epithelial cells having a suspicious morphology, and not on voided urine samples which enable analysis of a nucleus to cytoplasm ratio and identification of morphologically abnormal cells having a high nucleus to cytoplasm ratio as compared to normal transitional epithelial cells as in the currently amended claimed invention.

In view of the above arguments and remarks Applicants believe to have overcome the 35 U.S.C. §103(a) rejections.

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In view of the above amendments and remarks it is respectfully submitted that 72, 73, 82, 84, 87, 89, 91 and 93 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Enclosures:

- Request for Continued Examination (RCE)
- Petition for Extension of Time (Three Months)